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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/907,041	08/06/1997	JOEL S. GREENBERGER	76333/103	7766

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/907,041	Applicant(s) Joel S. Greenberger
	Examiner Shin-Lin Chen	Art Unit 1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Feb 10, 2003* .

2a) ☐ This action is **FINAL**. 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-32* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *1-11 and 17-32* is/are rejected.

7) X Claim(s) *12-16* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) X Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4) ☐ Interview Summary (PTO-413) Paper No(s).
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Official action mailed 3-27-03 (Paper No. 33) has been vacated. Applicant's amendment and Dr. Greenberger's declaration filed 2-10-03 have been entered. Claim 33 has been canceled. Claim 1 has been amended. Claims 1-32 are pending and under consideration.

Priority

1. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The relationship between the prior nonprovisional applications 08/136,079 and 08/484,836 must be indicated in the first sentence of the specification that claims the benefits of said nonprovisional applications.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-11, 17-26 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for radiation-resistant of murine melanoma cell line B16 via higher expression of γ-GTP, expression of a MnSOD transgene under control of the irradiation inducible egr-1 promoter that increases the radioresistance of 32D CL 3 hematopoietic

progenitor cells *in vitro*, and protection of cells from irradiation via administration of polynucleotide encoding MnSOD, MT, or gamma-GTP to a subject locally to the targeted site, does not reasonably provide enablement for a method for protecting any subject against an agent that produces toxic species including free radicals, superoxide anions, and heavy metals, by administering a pharmaceutical composition, comprising a polynucleotide encoding any protein other than MnSOD, MT, and gamma-GTP, to said subject to protect any targeted site *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-11, 17-26 and 30-32 are directed to a method for protecting a subject against an agent that elicits free radicals, superoxide anions, or heavy metal cations, said method comprising the steps of administering to said subject via local administration at the site to be protected from irradiation a pharmaceutical composition comprising a polynucleotide that encodes a protein transiently expressed in said subject, and a pharmaceutically acceptable vehicle for said polynucleotide.

The specification discloses the construction of recombinant adenoviral vectors Ad-MT, Ad-MnSOD, and Ad-γ-GTP; the expression of metallothionein (MT), manganese superoxide dismutase (MnSOD), and γ-Glutamyltranspeptidase (γ-GTP) in rat lung epithelium *in vivo*, and the function assay for MT, MnSOD, and γ-GTP proteins. The specification discloses expression of greater levels of γ-GTP in murine melanoma cell line B16 renders the cell line less sensitive to

γ-irradiation, and expression of a MnSOD transgene under control of the irradiation inducible egr-1 promoter increases the radioresistance of 32D CL 3 hematopoietic progenitor cells *in vitro*.

The claims encompass protecting a subject from an agent producing toxic species by administering a pharmaceutical composition comprising a polynucleotide encoding any protein that is able to neutralize said toxic species *in vivo*. The state of the art regarding a protein or a polynucleotide encoding said protein capable of neutralizing or eliminating free radicals, heavy metals, or superoxide shows that only MnSOD, MT and gamma-GTP have been discovered to have activity of neutralizing or eliminating free radicals, heavy metals, or superoxide. No other protein or polynucleotide encoding said protein has been disclosed in the art to have such activity. The specification fails to provide adequate guidance and evidence that proteins or polynucleotides encoding said proteins other than MnSOD, MT and gamma-GTP can neutralize or eliminate free radicals, heavy metals, or superoxide so as to protect any targeted site in a subject *in vivo*. There is no evidence of record that a polynucleotide encoding a protein other than MT, MnSOD, or gamma-GTP has the activity of neutralizing or eliminating toxic species, such as free radicals, heavy metals, and superoxides, and administration of said polynucleotide to a subject can provide protection of a target site in said subject from said toxic species. Different proteins have different chemical structures, physical properties and biological functions and whether said proteins have the activity of neutralizing or eliminating free radicals, heavy metals, and superoxides would require identification of the polynucleotides encoding said proteins, characterization of said proteins, trail and error determination of whether said proteins have the

activity of neutralizing or eliminating toxic species, such as free radicals, heavy metals and superoxides, and trial and error determination of whether said proteins or polynucleotide encoding said proteins can protect target sites in a subject from toxic species after local administration at the site to be protected *in vivo*. Therefore, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 27 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cousens et al., 1988 (US 4,751,180).

Claim 27 is directed to a pharmaceutical composition comprising a polynucleotide that encodes a protein that is capable of neutralizing or eliminating toxic species, such as a free radical, a superoxide anion, or a heavy metal, and a pharmaceutically acceptable vehicle for said polynucleotide.

Cousens teaches construction of a yeast expression plasmid pYSI1 containing the human SOD gene fused to the N-terminal of human proinsulin gene under the control of GAP promoter.

Cousens discloses a pBR322-derived expression plasmid phSOD which contains a complete cDNA sequence coding for hSOD (column 7). Cousens also teaches construction of expression vector for SOD-p31 fusion protein by using pS14/39-2 vector containing SOD gene fused to proinsulin gene under the control of ADH-2/GAP promoter and resuspends the plasmid in TE buffer (column 12). The TE buffer is considered a pharmaceutically acceptable vehicle. Thus, claim 27 is anticipated by Cousens.

6. Claims 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Hartman et al., 1988 (EP 0284105).

Claims 27 and 28 are directed to a pharmaceutical composition comprising a polynucleotide that encodes a protein that is capable of neutralizing or eliminating toxic species, such as a free radical, a superoxide anion, or a heavy metal, and a pharmaceutically acceptable vehicle for said polynucleotide. Claim 28 specifies the polynucleotide encodes a gamma glutamyl transpeptidase (gamma-GTP), a manganese superoxide dismutase (Mn-SOD), or a metallothionein (MT).

Hartman teaches construction of a plasmid pMSE-4 containing a human manganese superoxide dismutase (hMnSOD) coding region under the control of lamda P_L promoter, and use of said plasmid to transfect E. coli cells for producing recombinant hMnSOD. The buffer solution for the plasmid is considered a pharmaceutically acceptable vehicle. Thus, claims 27 and 28 are anticipated by Hartman.

7. Claims 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Ishiye et al., 1992 (FEMS Microbiology Letters, Vol. 97: 235-241).

Claims 27 and 28 are directed to a pharmaceutical composition comprising a polynucleotide that encodes a protein that is capable of neutralizing or eliminating toxic species, such as a free radical, a superoxide anion, or a heavy metal, and a pharmaceutically acceptable vehicle for said polynucleotide. Claim 28 specifies the polynucleotide encodes a gamma glutamyl transpeptidase (gamma-GTP), a manganese superoxide dismutase (Mn-SOD), or a metallothionein (MT).

Ishiye teaches construction of an expression vector containing coding sequence of E. coli HB101 gamma-glutamyltranspeptidase (GGT) and use of said plasmid to produce recombinant GGT protein. The buffer solution containing the expression vector expressing GGT is considered a pharmaceutically acceptable vehicle. Thus, claims 27 and 28 are anticipated by Ishiye.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartman et al., 1988 (EP 0284105) in view of Nabel et al., 1994 (Anals New York Academy of Sciences, Vol. 714, p. 247-252).

Claims 27 and 29 are directed to a pharmaceutical composition comprising a polynucleotide that encodes a protein that is capable of neutralizing or eliminating toxic species, such as a free radical, a superoxide anion, or a heavy metal, and a pharmaceutically acceptable vehicle for said polynucleotide. Claim 29 specifies the pharmaceutically acceptable vehicle is a liposome, an adenovirus vector, or a ligand-DNA conjugate.

Hartman teaches construction of a plasmid pMSE-4 containing a human manganese superoxide dismutase (hMnSOD) coding region under the control of lamda P_L promoter, and use of said plasmid to transfect E. coli cells for producing recombinant hMnSOD. The buffer solution for the plasmid is considered a pharmaceutically acceptable vehicle.

Hartman does not teach using adenovirus vector or liposome as a pharmaceutically vehicle.

Nabel teaches using retrovirus, adenovirus, adenoviral conjugates, and cationic liposomes for delivery of foreign DNA into vascular cells *in vitro* and *in vivo* (e.g. p. 247). Nabel teaches the use of those vectors for gene delivery in gene therapy *in vivo*.

It would have been obvious for one of ordinary skill at the time of the invention to substitute the plasmid as taught by Hartman with adenovirus vector or liposome as taught by

Nabel in order to introduce the human MnSOD into target cells, such as vascular cell, and for gene delivery in gene therapy as taught by Nabel with reasonable expectation of success.

It should be noted that the term "pharmaceutical" does not carry weight in 102(b) or 103(a) rejection.

Conclusion

10. Claims 1-11 and 17-32 are rejected. Claims 12-16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

SLC/dlr